REMARKS/ARGUMENTS

This case has been carefully reviewed and analyzed in view of the Office Action dated 4 April 2007. Responsive to this Action, Claim 1 has been amended for further prosecution with other Claims remaining pending. It is believed that with such amendment of Claim 1 there are further clarification of their recitations. Claim 25 has been canceled. No new matter is introduced in the application.

In the Office Action, the Examiner rejected Claim 1 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Accordingly, Claim 1 limitation "phosphatidylcholine" has been canceled to provide the necessary clarification thereto. It is now believed that the Claims particularly point out and distinctly claim the subject matter that the Applicant regards as the invention.

In the Office Action, the Examiner rejected Claims 1-24, 26-28, and 30 under 35 U.S.C. § 102(b) as being anticipated by Slater et al., U.S. Patent No. 6,355,268. The Examiner also rejected Claims 1-30 under 35 U.S.C. § 103(a) as being unpatentable over Slater et al. by itself or in combination with Zalipsky et al., U.S. Patent No. 6,051,251. Claim 25 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Slater et al. by itself or in combination with Zalipsky et al. as set forth above, further in view of Papahadjopoulos et al., U.S. Patent No. 6,426,086. Claims 27-29 were rejected under 35 U.S.C. § 103(a) as being

unpatentable over Slater et al. by itself or in combination with Zalipsky et al. as set forth above, further in view of Barenholz et al., U.S. Patent No. 5,316,771.

Before discussing the prior art relied upon by the Examiner, it is believed beneficial to first briefly review the structure of the invention of the subject Patent Application, as now claimed. The invention of the subject Patent Application is directed to a process to increase extrusion speed for producing a liposome suspension. A process to produce a liposome suspension includes a pre-mixture to an alcohol solvent, wherein the mixture comprises: (i) a phospholipid compound comprising 40%-70% of the pre-mixture and selected from the group consisting of lecithin, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, sphingomyelin, phosphatidic acids, a di(C_{12}-C_{18})acyl derivative of any foregoing and a combination of any of the foregoing; (ii) a cholesterol comprising 10%-30% (w/w) of the pre-mixture; and (iii) a polyethyleneglycol derived compound comprising 15%-30% (w/w) of the pre-mixture and selected from the group consisting of PEG-PE, methoxy-polyethyleneglycol (mPEG)-PE, a di(C_{12}-C_{18})acyl derivative of either of the foregoing and a combination of any of the foregoing. The ratio of the alcohol solvent to the total amount of compounds listed in (i), (ii), and (iii) is greater than 5:1 for increasing extrusion speed and lowering extrusion pressure. The pre-mixture is mixed with an aqueous ammonium sulfate solution to form a mixture, where the ratio of the amount of the pre-mixture to the aqueous ammonium sulfate is 1:2~10 (v/v) for increasing extrusion speed and lowering

extrusion pressure. Next, the mixture is subjected to a pore extrusion treatment and forming a pre-liposome suspension. The pre-liposome suspension is dialyzed with a 5% to 10% sucrose aqueous solution, where a liposome suspension containing liposome particles suspended in the liposome suspension is obtained.

According to page 2 of the Office Action, Claims 1-24, 26-28 of the present invention are rejected under 35 U.S.C. § 102(a) as being anticipated by Slater et al. for the following reasons:

In line 20 of col. 7 through line 23 in col. 9 of the Abstract and Example 1 of the Specification, Slater, et al. reference disclosed a process of preparation of liposomes. The Examiner thinks the following features of Slater et al. reference cover the present invention.

1. The process involves mixing soy phosphatidylcholine, cholesterol and PEG-DSPE in a mole ration of 56.4: 38.3: 5.3 in ethanol at 65 degrees and mixing this mixture with an ammonium sulfate solution at 65 degrees.

2. The mixture is subjected to an extrusion process through an extruder.

3. The ammonium sulfate and ethanol are removed from the external bulk aqueous phase prior to loading the active agent by the diafiltration.

4. The active agent, Topotecan, is dissolved in 40ml of 10% sucrose solution and then remotely loaded.

5. The amounts of individual components in Slater et al. reference fall within the ranges claimed.

However, the main objective of the Slater et al. reference is to provide a topoisomeraser inhibitor composition to improve cancer therapy and to provide a liposome composition for administration of the topoisomerase inhibitor (column 2, lines 45-51). The Slater et al. reference asserts to solve the problem about water insolubility of camptothecin that hinders the delivery of the drug (column 1, lines 59-60). The conventional liposome mentioned in the Slater et al. reference could be quickly removed from the bloodstream by the reticuloendothelial system (column 2, lines 12-14). The main objective of the Slater et al. reference is not about a preparing method of liposome and merely comprises a conventional preparation method in example 1 (column 20, lines 31-63).

The extrusion process of the liposome preparation usually experiences difficulties at high extrusion pressure, for example 150-250 psi and low extrusion speed (about 0.1-0.2L/min). The present invention provides a production process of liposome suspension with a low pressure and a higher extrusion speed, 40-140 psi and 2.0-10 L/min (page 13, lines 13-16), which solves the problem. The extrusion speed of the present invention can even be increased to about 10 times the extrusion speed of the prior art. However, Slater et al. does not disclose or suggest any solutions to the problems, either the high extrusion speed or the low extrusion pressure.

Moreover, the present invention discloses a proper amount of the mixture, the alcohol solvent and the ammonium sulfate solution (page 19, claim 1 in steps (a) and (b)). In step (a) of claim 1, the ratio of the alcohol solvent to the total amount of the mixture is greater than 5:1(w/v). A preferred embodiment of the ratio in the present invention is greater than 7-10:1(w/v). Within the ratio range, the present invention is capable of decreasing the surface tension of the solution further to increase the extrusion speed of the extrusion process. The Slater et al. reference merely discloses dissolving the mixture in ethanol but does not describe using ethanol, for example, to decrease the surface tension of the solution or to increase the extrusion speed (example 1; column 20, lines 40-60). In addition, the diafiltration used for removing ammonium sulfate and the ethanol in the Slater et al. reference is hollow fiber tangential flow diafiltration that is different from the present invention that to dialyze the pre-liposome suspension with 5% to 15% sucrose aqueous solution.

The ratio of the alcohol solvent and the mixture described in the Slater et al. reference is "[t]he total lipid concentration in ethanol solution was 3.7g total lipid per 10mL ethanol" (column 20, lines 42-44), which is about 2.7:1. The ratio of the alcohol solvent and the mixture in the Slater et al. reference does not fall within the ratio range of the present invention, which is greater than 5:1.

The Slater et al. reference does provide for a ratio for alcohol solvent and some compounds for lipids. However, the Slater et al. reference is not directed to

a process for producing a liposome suspension where the ratio of the alcohol solvent to the total amount of compounds listed in (i), (ii), and (iii) is greater than 5:1 for increasing extrusion speed and lowering extrusion pressure. Also, the Slater et al. reference does not provide for mixing the pre-mixture obtained in step (a) of Claim 1 with aqueous ammonium sulfate solution to form a mixture, "...wherein the ratio of the amount of the pre-mixture obtained in step (a) to the aqueous ammonium sulfate solution is 1:2~10(v/v) for increasing extrusion speed and lowering extrusion pressure...", as clearly seen in now amended independent Claim 1. Thus, the Slater et al. reference does not provide for the elements as provided in now amended Claim 1 for the objects and purposes of the subject Application.

The Zalipsky et al. reference does not overcome the deficiencies of the Slater et al. reference. Zalipsky et al. discloses a liposome loading method using a boronic acid compound. The liposome suspension was prepared by dissolving the lipids in ethanol and drying the lipids to a thin film. The lipid film was hydrated with an ammonium sulfate solution to form liposomes, and the liposomes were extruded to obtain liposomes of about 100nm (column 9, lines 39-44). The main objective of the Zalipsky, et al. reference is not about the liposome preparing process as in the present invention but to provide a liposome loading procedure for drugs that in their native form are insufficiently lipophilic for remote loading.

However, the Zalipsky et al. reference is not directed to a process for producing a liposome suspension where the ratio of the alcohol solvent to the total amount of compounds listed in (i), (ii), and (iii) is greater than 5:1 for increasing extrusion speed and lowering extrusion pressure. Thus, as previously discussed for the Slater et al reference, the Zalipsky et al. reference fails to disclose or suggest for mixing the pre-mixture obtained in step (a) of Claim 1 with aqueous ammonium sulfate solution to form a mixture, "...wherein the ratio of the amount of the pre-mixture obtained in step (a) to the aqueous ammonium sulfate solution is 1:2~10(v/v) for increasing extrusion speed and lowering extrusion pressure...", as clearly seen in now amended independent Claim 1.

This conventional method requires drying the lipid after dissolving the lipid in ethanol to obtain the liposome. The production process of the present invention is an improved method that dissolves the mixture with a proper amount of alcohol solvent, then adds ammonium sulfate directly to form a liposome suspension without the drying process. Moreover, the preparation methods in the Zalipsky et al. and Slater et al. references mentioned dissolving lipid in ethanol then drying. Obviously, ethanol is merely used as a solvent for lipid. Neither of the two references discloses adding ethanol during the extrusion process. Not adding an alcohol solvent during the extrusion process will result in high extruding pressures and low extrusion speed that adversely influence liposome yield. Although the

ammonium sulfate removal method in the Zalipsky et al. reference is also dialysis, the preparation process of liposome is not the same as the present invention.

The Examiner further mentioned on page 4 that Claim 25 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Slater et al. by itself or in combination with Zalipsky et al. as set forth above and further in view of the Papahadjopoulos et al. reference.

The teachings of Slater et al. and Zalipsky et al. have been discussed above. What is lacking in Slater et al. and Zalipsky et al. is the lyophilization of the liposomes. Papahadjopoulos et al. teaches that liposomes can be lyophilized and the lyophilized product can be combined with a sterile aqueous solution prior to administration (col. 19, lines 33-36). To overcome the rejection under 35 U.S.C. § 103(a), the Applicant had canceled Claim 25.

On page 5 of the Office Action, the Examiner rejected Claims 27-29 under 35 U.S.C. § 103(a) as being unpatentable over Slater et al. by itself or in combination with Zalipsky et al. as set forth above and further in view of Barenholz et al.

The teachings of Slater et al. and Zalipsky et al. have been discussed above. What is lacking in Slater et al. and Zalipsky et al. is the teaching of the doxorubicin as the active agent in the liposome for the Slater et al. reference would have been obvious to one with the ordinary skill in the art with a reasonable expectation of success since the reference of Barenholz et al. shows the loading of

doxorubicin in the liposome containing ammonium sulfate (Fig. 3, examples and Claims). However, the Barenholz et al. reference discloses a method of amphiphatic drug loading in liposomes by ammonium ion gradient, which focuses on the drug loading method in liposome.

Moreover, Barenholz et al. never addresses the high pressure and the low extrusion speed caused during the extrusion process that is the main subject matter of the present invention. The preparation of liposome in the Barenholz et al. reference comprises 100mg of EPC dissolved in 5ml of chloroform being poured into a round bottom flask and adding 25mg of cholesterol. The chloroform was evaporated using a flask evaporator under reduced pressure until dry (column 16, lines 23-24). The multilamellar vesicle (MLV) obtained above was extruded 3 times through a 0.4 μm Nucleopore polycarbonate filter and 3 times through a 0.2 μm polycarbonate filter using a stainless steel extrusion cell under a pressure of 150 psi created by argon gas in a Millipore filtration unit (column 16, lines 29-34). Both problems with the drying process and the high pressure of 150 psi in the Barenholz et al. reference are taught in the conventional process of preparing liposome in the present invention and had been solved. In fact, Barenholz et al. reference teaches away from the present invention because Barenholz et al. reference teaches that it prepares liposomes at only high pressures. Although the Barenholz et al. reference also described doxorubicin as the active agent, the preparation process of liposome is not the same as the present invention.

Therefore, none of the four referenced Patents involve the subject matter of the present invention, which is a process increasing extrusion speed of preparing liposome suspension and the product produced thereby. To achieve the present invention by modifying the Slater et al. reference in view of either the Zalipsky et al. reference, the Papahadjopoulos et al. reference, or the Barenholz et al. reference would have been non-obvious to one having ordinary skill in the art.

The Examiner thinks that the distinction between lecithin and phosphatidylcholine in Claim 1 is unclear. Another name for phosphatidylcholine is lecithin. Therefore, the Applicant amended Claim 1 by canceling the word "phosphatidylcholine (PC)" to remove any possibility of confusion between lecithin and phosphatidylcholine.

The Applicant believes that the rejection to Claims 1-30 is overcome by the remarks and the amended independent Claim 1 with other remaining pending dependent claims. Therefore, the present invention is now believed to be patentable.

Thus, even the combination of Slater et al., Zalipsky et al., Papahadjopoulos et al., and Barenholz, et al. are not believed to make obvious the invention of the subject Patent Application as now defined by amended independent Claim 1.

The remaining Claims are all ultimately dependent upon now amended Claim 1 and are believed to be patentable over the prior art for at least the same reasons discussed above.

If there are any further charges associated with this filing, the Honorable Commissioner for Patents is hereby authorized to charge Deposit Account #18-2011 for such charges.

Respectfully submitted,
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